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ROTAVIRUS SEGMENT of Immunization Update 2006, August 10, 2006.

ANDREW KROGER: In February 2006 the Food and Drug Administration approved a new vaccine to prevent rotavirus infection. It has been almost 7 years since the first rotavirus vaccine was taken off the market because of safety concerns. ACIP voted to once again include rotavirus vaccine among those routinely recommended for children. So let’s begin with a little background on rotavirus disease.

Rotavirus is the most common cause of severe gastroenteritis in infants and young children in the U.S. The spectrum of rotavirus ranges from mild, self limited watery diarrhea to severe dehydrating diarrhea with vomiting and fever.

The illness can be fatal. Rotavirus infection is nearly universal, with almost all children infected by 5 years of age. Infection can occur at any age, but the most severe disease occurs among children 3 months to 24 months of age. This translates to about 3 million infections every year - equal to the number of cases of pertussis or measles prior to the availability of vaccines. Rotavirus accounts for more than 400 thousand physician visits, 200 thousand emergency department visits and 55 to 70 thousand hospitalizations each year among children younger than 5 years of age. An estimated 20 to 60 children die each year in the United States from rotavirus disease. Although rotavirus is usually considered a childhood disease it also causes gastroenteritis in travelers from developing countries, parents and persons caring for children with rotavirus diarrhea, immunocompromised persons, and the elderly.

Rotavirus diarrhea results in more than 250 million dollars in direct medical costs each year in the U.S., largely due to hospitalization. Total costs, including indirect costs, are more than 1 billion dollars a year. Efforts to produce a vaccine to prevent rotavirus gastroenteritis began in the 1980s. Vaccine viruses were created by a process known as genetic reassortment. This process causes nonhuman rotavirus strains to express human rotavirus antigens on their surface. Nonhuman rotaviruses are used as the basis for the reassortant viruses because they have low pathogenicity for humans, meaning they replicate but do not cause disease. The first rotavirus vaccine was licensed in the United States in 1998. This vaccine contained a rhesus monkey

parent strain with genes that expressed an antigen for the predominant serotypes of HUMAN rotavirus. This vaccine was taken off the market in 1999 because vaccine recipients had an increased risk of intussusception, a type of bowel obstruction, particularly after the first dose.

Some research suggested that the older the child when the first dose was administered the greater the risk of intussusception. This observation has affected recommendations for the NEW rotavirus vaccine. The new rotavirus vaccine is called RotaTeq and is produced by Merck. RotaTeq was licensed by the Food and Drug Administration in February 2006. It is provided in single dose tubes without a preservative. This rotavirus vaccine contains five strains of live rotavirus developed from human and bovine rotavirus strains. The vaccine is supplied as a liquid and is administered orally in a three dose series beginning at about 2 months of age. A dose is 2 milliliters, about half a teaspoon.

Studies to evaluate the safety, immunogenicity, and efficacy of RotaTeq have involved more than 68,000 infants in the United States and other countries. This is one of the largest vaccine trials ever conducted, and was necessary to evaluate the vaccine for possible rare adverse events, particularly intussusception. Clinical trials demonstrated RotaTeq to be effective. It was found to be 74% effective in preventing any rotavirus diarrhea. But the vaccine is 98% effective in preventing severe diarrhea. Effectiveness against rotavirus diarrhea of any severity and severe disease was still high in the second rotavirus season postvaccination. The vaccine reduced physician visits for diarrhea by 86%, and reduced rotavirus-related hospitalization by 96%.

The safety of RotaTeq with respect to intussusception was evaluated in more than 71 thousand children in a large trial designed specifically to evaluate the risk of intussusception. In the 42 days after vaccination 6 cases of intussusception were observed among vaccinated children and 5 cases occurred among placebo recipients. Within the one year follow-up period after administration of the first dose, 13 cases of intussusception were observed in the vaccine group versus 15 cases in the placebo group. These data show that there is a background incidence of intussusception in children of this age, but that children who received rotavirus vaccine were NOT more likely to develop intussusception than those of the same age who received an inactive placebo. In a subset of about 12,000 children there was a small increase- 1 or 2%- in vomiting, diarrhea,

pharyngitis and otitis media among vaccinated children but no increase in fever. No serious adverse events were observed. Bill?

BILL ATKINSON:
The Advisory Committee on Immunization Practices voted on recommendations for use of RotaTeq at its February 2006 meeting. The recommendations were published on August 11, 2006. The vaccine will be included on the 2007 childhood immunization schedule. ACIP recommends routine immunization of all infants without contraindications. The vaccine should be administered as a series of three oral doses at 2, 4, and 6 months of age. It should be given simultaneously with other vaccines given at these ages. The vaccination series may be started as early as 6 weeks of age. Here is the complicated part. The first dose of rotavirus vaccine should be administered between 6 and 12 weeks of age. Vaccination should NOT be initiated for infants older than 12 weeks of age because of insufficient data on safety of the first dose in older infants. The minimum interval between subsequent doses is 4 weeks. All 3 doses of vaccine should be administered by 32 weeks of age. Vaccine should NOT be administered after 32 weeks of age because of insufficient data on the safety and efficacy in infants after this age. There are at least 5 serotypes of rotavirus that may cause diarrheal disease in the United States. Also, infants may experience multiple episodes of rotavirus diarrhea. So infants documented to have had rotavirus gastroenteritis before receiving the full course of rotavirus vaccinations should still begin or complete the 3 dose schedule. This is because the initial infection may provide only partial immunity. Breast feeding does not significantly reduce the immunogenicity of rotavirus vaccine, so these children should be vaccinated as usual.

Rotavirus vaccine is a live virus vaccine, so contraindications to its use are similar to other live virus vaccines. As with all vaccines, a severe allergic reaction to a vaccine component or following a prior dose is a contraindication to further doses. Precautions to the use of rotavirus vaccine include altered immunocompetence from any cause, pre-existing chronic gastrointestinal disease such as malabsorption or Hirschsprung’s disease, a history of intussusception, and moderate or severe acute illness, including acute gastroenteritis. In general when precaution conditions are present the vaccine will not be given. However, clinicians may consider use of the vaccine on a case by case, risk and benefit basis. Andrew?

ANDREW KROGER:

There are limited data on the use of rotavirus vaccine among preterm infants – that is, infants born before 37 weeks gestation. There were very few preterm infants included in the clinical trials.

There is concern that preterm infants may be at increased risk of adverse reactions following vaccination because of lower levels of passively acquired maternal antibody. On the other hand, preterm infants may be at increased risk of hospitalization from diarrheal disease. Considering these potential risks and benefits ACIP supports the vaccination of a preterm infant if the infant is at least 6 weeks of age, AND is being or has been discharged from the hospital, AND is clinically stable. Vaccination should be deferred until discharge to avoid contamination of the newborn nursery with vaccine virus. Rotavirus vaccine virus replicates in the gut and can be shed in the stool of vaccinated infants. In clinical trials, shedding was observed as early as 1 day and as late as 15 days after a dose. Shedding of vaccine virus was detected in about 9% of recipients after the first dose, but in only 1 of more than 600 second and third dose recipients who were tested. The potential for transmission of vaccine virus has not been assessed. Additional data on transmission are needed. However, ACIP recommends vaccination of infants living in households with persons with altered immunocompetence, or women who are pregnant. Vaccination of the child will protect the immunocompromised household member from exposure to wild type rotavirus. The benefit outweighs the small risk of transmission of vaccine virus to the immunocompromised household member. To minimize potential virus transmission, all members of the household should employ measures such as good hand washing after contact with the feces of the vaccinated infant, such as after changing a diaper.

A related issue is exposure of healthcare personnel during administration of rotavirus vaccine or contact with vaccinated infants. Hand hygiene using soap and water or alcohol-based hand cleaners should already be standard practice wherever vaccines are being administered. This practice should minimize the risk of transmission of rotavirus vaccine virus during administration. Consequently, there are no restrictions on immunosuppressed or pregnant healthcare personnel administering the vaccine. Sometimes infants spit up or regurgitate oral vaccine. There are almost no data on the safety or efficacy of giving 2 doses, even partial doses, close together. Both the ACIP and the manufacturer recommend that you should NOT repeat

the dose if the infant spits out or regurgitates the vaccine. You should administer any remaining doses on schedule.

One other administration tip - most infants will be receiving multiple other vaccines at the same visit. We suggest you administer the rotavirus vaccine first, before administration of injected vaccines. Getting the vaccine into a calm child will be much easier than getting it into a child upset from multiple shots. RotaTeq is provided in a squeezable plastic dosing tube like this one, with a twist-off cap. It is designed to allow the vaccine to be administered directly to infants by mouth. Each tube contains a single 2 milliliter dose of the liquid vaccine. The liquid is a buffered-stabilized solution that is pale yellow in color but may have a pink tint. This formulation protects the vaccine virus from gastric acid and stabilizes the vaccine, allowing for storage at refrigerator temperatures up to 24 months. You should protect the vaccine from light by keeping the plastic tubes in the box until ready for use. Do not freeze this vaccine. Vaccine exposed to freezing temperature should not be used. Like other universally recommended vaccines, rotavirus vaccine will be included in the Vaccines For Children program. A Vaccine Information Statement has been developed and is available on the National Immunization Program website. We are pleased to finally have another rotavirus vaccine available in the United States. We hope that wide use of this safe and effective vaccine will help reduce the huge burden of rotavirus disease in the United States.

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